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## **Pain in amyotrophic lateral sclerosis**

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## **Abstract**

Pain is a largely neglected symptom in amyotrophic lateral sclerosis (ALS) although reported in a majority of patients. It occurs at all stages of the disease and can be an onset symptom preceding motor dysfunction. Pain is correlated with a deterioration of the patient's quality of life and increased depression. In the later stages of ALS, the pain severity can be such as to require increasing use of sedative-analgesic drugs and is among the events predicting clinical deterioration and death. The site of pain depends on the pain type or underlying mechanism, i.e. painful cramps (lower limbs, hands), nociceptive pain (shoulders, joints, pressure sores) or neuropathic pain (feet, lower limbs). Given the multifactorial nature of pain in ALS, different treatments have been suggested, ranging from non-steroidal anti-inflammatory agents, drugs for neuropathic pain, opioids and, most recently, cannabinoids, to physical therapy strategies and preventive assistive devices. Further understanding of the pathophysiology is crucial to drive assessment in clinical trials of therapeutic strategies targeted at specific mechanisms and studies of individually tailored therapies.

## Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease whose outcome is fatal within 2-4 years from onset.<sup>1</sup> The ALS degenerative process involves upper and lower motor neurons with onset usually at the bulbar or spinal levels, causing progressive loss of strength at limbs, dysphagia, dysarthria and respiratory failure. Motor neuron degeneration is the predominant cause of patient disability throughout all ALS stages and is eventually responsible for death. However, many patients also have involvement of extra-motor components, in particular the prefrontal cortex, associated with cognitive impairment or frontotemporal dementia,<sup>2,3</sup> and although central nervous system sensory structures are generally spared, some evidence for sensory system involvement comes from neuropathological,<sup>4,5</sup> imaging,<sup>6,7</sup> and clinical<sup>5,8,9</sup> studies, as well as from rodent models of ALS.<sup>10,11</sup>

Pain was quite a neglected symptom in ALS up until about ten years ago<sup>12</sup> owing to a misconception of the disease as purely of a motor nature, that leads clinicians not to ask their patients about pain,<sup>12,13</sup> as also has been the case with other non-motor symptoms. However, in the last decade, the variability of ALS between affected individuals has clearly emerged, and among the wide spectrum of neurological defects and adjunctive manifestations that have been investigated, several studies have focused on pain in ALS,<sup>13-18</sup> confirming earlier observations.<sup>19-21</sup> Furthermore, pain has been considered, mostly from a therapeutic point of view, in the main guidelines of ALS treatment,<sup>22,23</sup> being also the subject of a Cochrane review.<sup>24</sup> Nevertheless, the incidence, severity, distribution, underlying mechanisms and treatment of pain in ALS have not been completely addressed, mainly due to the lack of a standardized method for diagnosing pain, the relative lack of data regarding pain determinants, and confounding variables.

The importance of identifying and assessing pain in ALS patients cannot be overlooked. Pain has profound detrimental effects on ALS patients' and caregivers' quality of life<sup>14,18,25</sup> and there are initial indications that it may have prognostic significance.<sup>26,27</sup> Different types of pain might arise from different underlying mechanisms – e.g., primary causes of pain such as neuropathic pain could arise from the impairment of the somatosensory pathways, whereas secondary causes of pain, due to the effects of tissue damages, are mainly nociceptive – and understanding the pathophysiology of pain in ALS would be relevant to determine the best treatments for individual patients.

In this review, we summarise current understanding of pain in ALS and explore potential directions for future research. We first briefly describe the epidemiology of pain in ALS, before outlining the key clinical characteristics, including the relation between pain and other comorbidities. We then discuss potential underlying mechanisms, with assessment of the evidence for neuropathic, nociceptive, and central sensitisation origins of pain in this disease. Genetic correlates of pain are discussed and, finally, we review current management strategies and emphasise the need for more rigorous studies of treatments for pain in ALS.

### **Epidemiology of pain in ALS**

There are few systematic studies on pain in ALS and only three longitudinal studies (Supplementary Table 1). The reported frequency of pain in ALS varies greatly, from less than 15%<sup>20,28,29</sup> up to 85%.<sup>14,17,25,30-33</sup> This large variability is related to the different study designs and settings, and the different instruments used to identify and measure pain. Moreover, the number of ALS patients included in these studies is rather small, ranging from 7<sup>33</sup> to 424.<sup>17</sup> Interestingly, larger observational studies on the natural history of ALS do not even mention pain among the clinical features of the disease.<sup>34,35</sup> It suggests that the investigational setting, as well as the definition of pain, the tools used and, likely, the attention that neurologists and ALS patients pay to pain may all have a significant impact on the determination of its epidemiology, resulting in quite opposite conclusions. For instance, two studies, one randomized clinical trial<sup>18</sup> and one study focused on coping,<sup>36</sup> both indicated that loss of strength, ability to move and fatigue, but *not* pain, were perceived as the most significant non-bulbar symptoms. In net contrast to this, studies focusing on pain reported it as one of the most significant causes of suffering among ALS patients,<sup>14,21</sup> also as compared with other neuromuscular diseases.<sup>32</sup> Finally, it should be considered that cognitive impairment limits the reliability of pain assessment and, therefore, the interpretation of epidemiological studies.

### **Assessment of pain in the clinical setting**

Despite the high frequency of pain in ALS and its negative impact on patients' quality of life, both the Practice Parameters of the American Academy of Neurology<sup>22</sup> and the European Guidelines on the Clinical Management of ALS<sup>23</sup> discuss its treatment in ALS but do not suggest a proactive screening of this symptom during the course of the disease. In an online survey on pain in USA, in which only one-third of physicians from ALS clinics responded,<sup>37</sup> 92% stated that pain was routinely assessed in all practices, not only by the caring neurologist but also by other team

members like nurses and physical and occupational therapists. Pain was usually assessed by open-ended questions. Less than 20% of ALS clinics used rating scales or questionnaires to assess pain. Almost 65% of physicians reported the need for better pain management practices and more than one-third emphasized the need for better training. This indicates that there is a sufficient awareness on the issue of pain among ALS multidisciplinary teams, but also that pain is frequently not dealt with standard protocols and adequate training.

In studies that have formally assessed pain in patients with ALS, the most frequently used measure has been the Brief Pain Inventory questionnaire,<sup>14,17,25,30,32</sup> a self-report tool that rates current pain, its intensity over the previous week and the interference with mood, physical, working and social activity, and sleep. Further tools such as the Neuropathic Pain Scale, the short-form McGill Pain Questionnaire, the Neuropathic Pain Symptom Inventory, the Neuropathic Pain Diagnostic Questionnaire and other questionnaires were used in other studies.<sup>28,31</sup> These questionnaires are validated and can be used as discriminative and descriptive instruments to screen patients, though their ability in diagnosing the different forms of pain in individual patients is arguable.<sup>38</sup>

Moreover, pain perception is known to be strongly affected by attention, hypervigilance and context,<sup>39</sup> all of which can variably influence the experience of pain and, therefore, how pain is recorded and to what degree it interferes with life.

### **Characteristics of pain in ALS and relation to comorbidities**

In patients with ALS, there is great variability in the clinical manifestations and localisation of pain (Figure 1), which depend on whether the pain represents primary mechanisms or results from the secondary effects of motor degeneration (see below for discussion of mechanisms). Pain severity and the presence and nature of pain over the disease course also vary between individuals, and in some cases pain is evident before the presence of motor symptoms. Pain can be acute or chronic (when continuous for at least 3 months or longer) in ALS. In case-control studies, pain has been reported to be significantly more frequent in ALS patients than in healthy and neurological age- and sex-matched controls,<sup>14,25,30</sup> indicating that pain in ALS is not merely related to comorbid disorders; nevertheless, assessment of comorbid disorders is crucial for the accurate interpretation of pain assessments in these patients. Genetic factors are known to influence pain onset and course, as well as individual response to analgesics. The role of ALS causative genes like *SOD1* and *C9orf72*, as well as that of pain-related genes like sodium channels in influencing in ALS

has not been investigated and is still little known. This issue is discussed in the supplementary file 1.

### *Types of pain*

Primary causes of pain in ALS include pain with neuropathic features such as spontaneous (e.g. burning, tingling, paroxysmal shooting pain) and evoked (e.g. allodynia, hyperalgia, aftersensation) symptoms, and can affect distal extremities and can be focal or diffuse. However, two clinical studies on neuropathic pain in ALS provide no or only weak evidence for this pain type in patients with ALS: in a case-control study, no patients scored high enough in the Pain Detect Questionnaire to reach the neuropathic threshold, and 80% of ALS patients scored less than 12/38, suggesting that their pain was nociceptive in nature,<sup>25</sup> while a cross-sectional study showed that only 9% of 96 patients with pain had features of neuropathic pain according to the Neuropathic Pain Diagnostic Questionnaire and higher pain intensity score.<sup>40</sup> Spasticity and cramps are other common primary causes of pain in ALS. Cramps are the major cause of pain in about one-quarter of patients, mainly with the spinal form.<sup>41</sup> They originate from instability of motor units at the level of distal motor nerves as demonstrated by needle electromyography studies and are typically associated with muscle denervation.<sup>42</sup>

The above-mentioned case-control study<sup>25</sup> reported itch among non-motor symptoms in about 35% of ALS patients, but it did not provide data on possible correlation with opioid therapy that was followed by 29% of patients, making unclear the relationship with ALS. Indeed itch, besides occurring in a wide range of systemic, dermatological and neurological illnesses,<sup>43,44</sup> can be a side effect of drugs like opioids and chloroquine.<sup>45</sup>

Secondary (mainly nociceptive) causes of ALS pain develop as disease progresses, whereby atrophy and weakness of muscles and prolonged immobility cause degenerative changes in connective tissue, bones and joints leading to musculoskeletal pain. Joint contractures are common and ALS patients frequently experience shoulder pain due to loss of strength of the periscapular muscles.<sup>46</sup> Skin pressure can cause decubitus ulcers, though these are rather uncommon despite the poor mobility. Some patients also complain of diffuse and unexplained pain, mainly in the late phase of the disease.

Non-invasive ventilation (NIV) is another cause of secondary pain or discomfort due to interface-related problems with the mask. Skin lesions, particularly ulcers on the nasal bridge, are painful

complications and common reasons for poor adaptation or NIV failure. In a study on 37 ALS patients on invasive ventilation,<sup>47</sup> more than 80% of patients reported to suffer from pain due to remaining in the same physical position for prolonged periods of time; 70% referred that the ventilator hose weighing or pulling on the throat caused severe pain, and 50% reported the experience of pain associated with suctioning of saliva or phlegm. The latter two causes of pain are of particular interest because often overlooked by caregivers and physicians.

Moreover, a recent study in ALS suggested that mechanical ventilation, while corrects hypoventilation and alleviates dyspnoea, might increase the susceptibility to pain in terms of reduced pain pressure threshold.<sup>48</sup> Dyspnoea is known to activate the diffuse nociceptive inhibitory control as demonstrated by its inhibitory effect on painful stimuli (e.g. laser evoked potentials)<sup>49</sup> and nociceptive spinal flexion reflex (e.g. nociceptive RIII reflex).<sup>50</sup> Although preliminary and not yet supported by focused clinical studies, these data<sup>48</sup> suggest that a careful assessment of pain may be warranted in ALS patients after starting the mechanical ventilation.

#### *Localisation of pain*

Studies including the assessment of pain distribution in ALS did not reveal a specific localization of symptoms, which could involve distal and proximal sites of upper and lower extremities and the back<sup>14,15,17,25,30,31</sup> or be widespread.<sup>32</sup> Conversely, studies investigating small nerve fibre loss reported cases of painful symptoms predominantly in the feet,<sup>28,29</sup> suggesting that pain recording in ALS may be biased by the study design. However, almost all studies agreed that pain is less common in the bulbar form of ALS.<sup>14,15,41</sup> implying that skeletal muscle involvement may be an important risk factor.

#### *Severity of pain*

Pain intensity was recorded as mild (e.g.  $\leq 3$  on a 0-10 rating score) in most studies,<sup>14,17,25,30</sup> but in other studies patients reported higher scores - from moderate<sup>32</sup> to severe or unbearable pain.<sup>31</sup> In keeping with these findings, one study demonstrated that pain intensity did not correlate with the Pain Interference Score,<sup>17</sup> suggesting that pain itself, but not its severity, may be a major determinant of suffering in ALS patients. However, more than 50% of ALS patients complaining of pain were reported to use pain drugs<sup>14,17,25,30,40,46</sup> more frequently than population-based controls, indicating that when pain is detected in ALS patients is more likely to be actively treated than in the general population.<sup>14</sup>



### *Pre-diagnostic ALS pain*

It has been reported that pain may anticipate motor impairment by two or more years, although a direct causality has not been convincingly proven.<sup>20,51</sup> Painful cramps in the legs and hands are often present at the onset of disease (Panel 1).<sup>52</sup> Similarly, shoulder pain has been reported as the presentation symptom in about 10% of ALS patients, often associated with proximal upper limb weakness, but not with age, gender, manual labour, prior shoulder problems, ALS phenotype, or initial region of involvement.<sup>46</sup> In a case-control study,<sup>25</sup> 25% of ALS patients complaining of pain had pain before the onset of disease. In the largest survey on this topic,<sup>17</sup> of the 318 patients complaining of pain from a cohort of 424 patients, half reported that pain started before ALS onset as low back pain, arthritis, headache, as pain from surgery, accident, injury, or cancer, or as other forms of pain. Nevertheless, 82% of the same sample reported that the pain experienced was due to ALS, and 34% that it was the presenting symptom of ALS.<sup>17</sup> These figures, apparently lacking internal reliability, are likely explained by the evidence that most patients reported the worst pain as that of the past week,<sup>17</sup> which possibly influenced their overall responses to the survey. However, no systematic studies on pain and cramps in the pre-diagnostic phase of ALS have been performed. Most recently, an epidemiological study<sup>53</sup> showed that ALS patients at least two years before onset of the disease made more frequent use, compared to the general population, of central nervous system drugs (mainly gabapentin) commonly used as a treatment for neuropathic pain (hazard ratio 1.84; 95% confidence interval 0.99-3.42), suggesting that sensory disturbances may precede the onset of motor impairment.

### *Progression of pain through the disease course*

Although some studies suggested that pain is more frequent in the later stages of disease and found a correlation with the progression of functional impairment,<sup>14,15,18,21</sup> others did not find a difference in frequency between the early and late phases of the disease,<sup>15,25</sup> or emphasized a lack of correlation between ALS duration and pain severity.<sup>30,31</sup> These differences among studies are mostly related to their cross-sectional design, which does not allow to identify the natural history of pain during the course of the disease. A longitudinal study on physical and psychological status in ALS,<sup>54</sup> which used the Visual Analogue Scale, found that pain intensity increased by 1 point from the first to the last visit, a median of 104 days later (range 35 to 846 days). This study showed that, in contrast to other symptoms such as depression and feeling of burden, patients and caregivers gave a similar rating of pain near the end of life.

During the last month of life, 52% of patients have reported pain as present almost all the time or constant, and rated it as moderate or severe.<sup>55</sup> Studies on ALS patients admitted to a hospice reported that pain was present in more than 75% of patients and that most of them had uncontrolled pain before the admission.<sup>56</sup> The presence of pain, as assessed by the Bodily Pain domain of the Short Form (36) Health Survey (SF-36), did not influence the decision of ALS patients to accept or decline non-invasive ventilation (NIV).<sup>57</sup> In a series of ALS patients treated with invasive ventilation (tracheostomy), the increase of pain and the need of sedative-analgesic drugs, together with cognitive-communication impairment, local infections and sepsis, pressure sores, and the need for indwelling catheters, were found to be events predicting the clinical deterioration leading to death.<sup>58</sup> The frequency of pain and, to a lesser extent, its severity is one of the reasons for requesting access to euthanasia or assisted suicide in ALS patients.<sup>59,60</sup>

### *Comorbidities*

The correlate of pain is reported to be, not unexpectedly, the deterioration in patients' quality of life.<sup>14,25</sup> However, when depression is included as a covariate in the statistical analysis, the effect of pain intensity is no longer significant.<sup>31</sup> Not surprisingly, pain is reported to be significantly more common in depressed ALS patients<sup>61</sup> and depression to be more frequent in ALS patients complaining of pain.<sup>62</sup> The co-presence of pain and depression has been reported to correlate with a poorer quality of life in ALS patients.<sup>31</sup> Pain is known to have a high frequency among patients diagnosed with depression, with a prevalence of up to 75%,<sup>63</sup> and to interfere with physicians' ability to identify depression.<sup>64</sup> On the other hand, depression has been recorded in up to 86% of patients with chronic pain.<sup>65</sup> Therefore, the lack of data regarding mood disturbances in some studies that focused on pain in ALS<sup>14,15,18,30</sup> may limit the interpretation of the results. This latter consideration may be true also for the larger group of neuromuscular diseases, including inherited myopathies and neuropathies, amongst which ALS patients were found to have a relatively lower frequency of pain, compared also with post-poliomyelitis syndrome.<sup>32</sup> Depression is very frequent in neurodegenerative diseases<sup>66</sup> including ALS,<sup>61,67</sup> and at least 30% of ALS patients have been reported to follow anti-depressant therapy.<sup>61</sup> A recent prospective study<sup>67</sup> of a large ALS cohort followed-up for 8 years reported the occurrence of early moderate or moderate-severe depression in 47% of patients, which correlated with disease severity, and significantly impacted survival and quality of life. However, the study emphasized that depression did not progress along with motor deterioration, confirming previous findings on the lack of correlation between

depression and duration of the disease.<sup>61</sup> Considering the close correlation between mood disturbances and pain, this latter finding may explain why ALS patients are observed to complain of pain at any stage of the disease.<sup>15,30,31</sup>

Differently from depression, other comorbid emotional symptoms, such as anxiety, apathy, and emotional lability, have never been studied in relation to pain in ALS.

In about 50% of ALS cases a comorbidity of motor symptoms with frontotemporal dementia (FTD) or milder form of cognitive impairment has been described.<sup>68</sup> While no studies on pain in patients with comorbid ALS and FTD have been performed, a recent study showed that 40% of patients with pure behavioural variant FTD had blunted responsiveness to painful stimuli and temperature, particularly patients carrying the *C9orf72* mutation. Using MRI voxel-based morphometry analysis pain and temperature symptoms were associated to a right-lateralized network including anterior temporal cortex, posterior thalamus and insula, indicating an altered processing of somatosensory signals.<sup>69</sup> Such failure to interpret pain and temperature variations can put patients at risk of injuries. Due to the pathogenic relevance of *C9orf72* mutation in ALS, this observation should be investigated in larger series of patients with *C9orf72* mutations.

### **Mechanisms of pain in ALS**

In patients with ALS, the relationship between the unpleasant sensory and emotional experiences that pain entails and the progressive degeneration of upper and lower motor neuron degeneration along with the involvement of other nervous system structure is poorly understood. According to the cross-sectional studies discussed, much of the chronic pain in ALS seems to result as a side effect of the motor impairment of ALS (i.e., secondary pain); however, this does not seem to explain all pain types in these patients. The pathophysiological origin of primary (mainly neuropathic) as well as secondary (mainly nociceptive) pain therefore needs to be explored, considering also the possibility of a maladaptive sensory response (central sensitisation) in these patients. Knowledge of the mechanisms of pain can be relevant in clinical practice to decide the analgesic treatments and, possibly, preventive strategies, and understanding of the pain type should be approached using currently accepted diagnostic criteria for neuropathic pain,<sup>70</sup> nociceptive pain,<sup>71</sup> and central sensitisation.<sup>72,73</sup>

**Neuropathic pain.** Prerequisite to the diagnosis of neuropathic pain is the evidence of a lesion or disease affecting the somatosensory system.<sup>70</sup> CNS sensory structures are generally spared in ALS, although the involvement of the posterior columns of the spinal cord has been demonstrated by neuropathological studies in some cases of familial ALS<sup>4,5</sup> and by MRI alone<sup>6</sup> or combined with somatosensory evoked potentials in some sporadic ALS patients.<sup>7</sup> Clinically, there are occasional reports of sensory involvement.<sup>5,8,9</sup> A Wallerian-like degeneration of dorsal root and dorsal funiculus axons has been described in the *SOD1* mice model of ALS.<sup>10</sup>

Based on the current definition of neuropathic pain,<sup>70</sup> the evidence of sensory nerve fibre damage, if associated with a plausible clinical picture, could support the diagnosis of neuropathic pain. The distribution of symptom and signs should be used to define the level of certainty of neuropathic pain, and validated tests (e.g. nerve conduction studies and/or skin biopsy) should be used to demonstrate the relationship with a lesion or a disease.<sup>70</sup> Sensory nerve conduction study (NCS) investigates large myelinated fibres transducing proprioceptive and touch sensation, whereas small unmyelinated and thinly myelinated nerve fibres conveying thermal and nociceptive stimuli can be easily examined by skin biopsy with quantification of intraepidermal nerve fibre (IENF) density (Panel 2).<sup>74</sup>

This approach, however, has not been systematically used for the assessment of neuropathic pain in ALS. Indeed, two clinical studies that have investigated the neuropathic origin of pain in ALS patients using questionnaires that can be used as discriminative or descriptive instruments, either did not find evidence for neuropathic pain<sup>25</sup> or identified only a minority of patients with features of neuropathic pain (i.e., numbness, burning, tingling, etc.,<sup>40</sup> but did not confirm findings in these patients with nerve conduction studies or skin biopsies.

In studies of sensory nerve fibre damage, altered sensory NCS findings, most commonly subclinical, have been described in up to 30% of patients with an eventually confirmed diagnosis of ALS,<sup>9,75</sup> although this percentage decreased to about 4% in more recent studies.<sup>28,29,76</sup> A recent study<sup>77</sup> suggested that sensory NCS abnormalities could be more frequently identified if distal nerves (e.g. dorsal sural and medial plantar) rather than conventional nerves (e.g. sural and median) are recorded, with 8 of 18 ALS patients showing abnormalities on conventional sensory NCS compared with 12 of 18 patients on distal sensory NCS.

The degeneration of IENF, which are terminal nociceptors, highly increases the risk of developing neuropathic pain in patients with peripheral neuropathy.<sup>74</sup> Recent studies<sup>28,76</sup> reported that more

than 50% of ALS patients have small fibre neuropathy, but they did not investigate the correlation with pain<sup>76</sup> or find a correlation with neuropathic pain as assessed by questionnaires.<sup>28</sup> The study of a larger cohort of 51 ALS patients, including genetically defined cases, and 6 facial onset sensory and motor neuronopathy (FOSMN) patients,<sup>29</sup> confirmed that small nerve pathology in part of the clinical picture in 75% of ALS cases but did not find any correlation with genotype, phenotype (e.g. bulbar versus spinal), duration of disease, disability, sensory NCS, sensory symptoms and, in particular, pain that 4 patients reported. A further study based on multiple skin biopsies confirmed these findings and demonstrated the asymptomatic involvement of autonomic nerves and Meissner corpuscles in ALS.<sup>26</sup> The biological bases of IENF degeneration have been investigated in SOD1<sup>G93A</sup> mouse models of ALS demonstrating that a misplacing of the peripherin specifically accumulates in small-size dorsal root ganglion neurons, from which IENF arise, and alters the homeostasis of neurofilaments. This phenomenon occurs since the asymptomatic phase of the disease, is likely intrinsic to its pathophysiology.<sup>11</sup>

Despite the evidence of damage to the somatosensory system based on NCS and skin biopsy findings, the lack of correlation with the clinical feature does not support the hypothesis that pain in most ALS patient may have a neuropathic nature, although further focused studies are warranted.

***Nociceptive pain.*** Nociceptive pain is defined as arising from actual or threatening damage to non-neural tissue or from the activation of peripheral nociceptors in response to mechanical or other noxious stimuli.<sup>71</sup> It is the most common type of pain that follows inflammatory conditions, surgery, arthrosis and traumatic injuries. Patients with impaired shoulder joint mobility due to upper arm weakness can suffer from typical nociceptive pain, whereas patients with chronic low-back pain can have a mixed neuropathic and nociceptive pain.

Based on the reports that pain in ALS is frequently associated with reduced mobility and skin pressure, and that more frequently involves extremities, back, shoulders and neck (panel 3),<sup>14,15,17,20,21,30,31</sup> it may be conceivable considering a predominantly nociceptive nature. This view is keeping also with the good response to non-steroidal anti-inflammatory drugs (NSAIDs) that are the first line of treatment of pain in ALS patients,<sup>24</sup> and that are not effective in neuropathic pain.<sup>78</sup> However, the nociceptive origin of pain in ALS has never been systematically investigated, and the diagnosis has been achieved by exclusion in studies primarily focused on neuropathic pain.<sup>25</sup> Moreover, the hypothesis that pain in ALS may be caused by the reduced mobility should

suggest a correlation with the duration of the disease that, however, is still a controversial issue.<sup>14,15,17,40,79</sup> Therefore, although some patients with evidence of tissue or joint damage can be definitely diagnosed with nociceptive pain, others might acquire an enhanced sensory response to normal inputs normally evoking innocuous sensations driven by central sensitization.

**Central sensitisation.** Basing the analysis of pain in ALS on the available literature, it becomes clear that neither neuropathic nor nociceptive mechanisms can completely explain its nature, occurrence and maintenance. A further phenomenon known as central sensitisation may play a role. Central sensitisation is currently thought to have a key role in various clinical conditions dominated by chronic pain<sup>80</sup> including musculoskeletal disorders<sup>80</sup> and is part of a newly proposed algorithm for chronic low back pain.<sup>81</sup> It can complicate both neuropathic and nociceptive pain as the consequence of temporal, spatial and threshold changes of the signalling conveyed throughout the somatosensory system.

Two definitions are currently recognised: an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity<sup>72</sup> and an augmented responsiveness of central nervous system (CNS) neurons to normal or subthreshold afferent inputs that evoke innocuous sensations.<sup>73</sup> Despite some intrinsic distinctions, both the definitions converge toward the concept of an abnormally enhanced nociceptive response in the CNS. Seminal papers<sup>82,83</sup> have demonstrated that central sensitization can cause the spread of pain sensitivity across peripheral nerve territories, resulting in painful symptoms that are not necessarily driven by noxious stimuli or whose contribution was not necessary to produce pain, because they can induce a central amplification of sensory inputs determined by the state of excitability of CNS neurons. This complex networking is summarized by the concept of heterosynaptic potentiation that represents a condition where sensory inputs can amplify, even after have ended, subsequent responses of other non-stimulated non-nociceptive or nociceptive neurons that once triggered can persist over some time or require a very low level of nociceptive input to be maintained.<sup>72</sup>

No study has approached the issue of diffuse pain in ALS through the analysis of central sensitization, also due to the current lack of definite diagnostic tools. However, it would be a conceivable mechanism to consider based on the involvement of brain areas such as the prefrontal cortex, anterior cingulate cortex, insula, amygdala, thalamus and midbrain in chronic pain and in cognitive-emotional and affective processing of sensations,<sup>39</sup> and whose functional impairment has been observed to occur also in ALS.<sup>84,85</sup>

## **Treatment**

The ultimate need of ALS patients suffering from pain is to reduce its intensity and if possible prevent chronification of pain. After defining the cause of pain, the appropriate treatments including pharmacological and non-pharmacological interventions should be adopted, following guidelines when available, with the aim to provide patients with personalised therapies.

Pharmacological treatments are the main approaches for neuropathic and other types of primary pain, in combination with non-pharmacological approaches for some symptoms such as spasticity, whereas non-pharmacological strategies are generally more effective for secondary sources of pain. A summary of pain treatments in ALS is reported in Table 1.

**Table 1: Studies of clinical use and effectiveness of pharmacological treatments for pain in ALS**

Drug	Study design	Number patients or centres	Results	Main target	Mechanisms of action	Posology	Side-effects	Contraindications	Comments
<b>Neuropathic pain (extremities)*</b>									
Gabapentin <sup>78</sup>	EFNS guidelines	N/A	Effective in various causes of neuropathic pain	Voltage-dependent calcium channel $\alpha 2/\delta$ subunits	Inhibits voltage-gated calcium channels; decrease glutamate, substance P and CGRP release <sup>86</sup>	900-3,600 mg per day	Dizziness, fatigue, drowsiness, ataxia, peripheral oedema, nystagmus, tremor, weight gain	None	Guidelines focused on neuropathic pain of any cause and not on ALS
Pregabalin <sup>78</sup>	EFNS guidelines	N/A	Effective in various causes of neuropathic pain	Voltage-gated calcium channel $\alpha 2/\delta$ subunits	Inhibits voltage-gated calcium channels; decreases glutamate release; modulates potassium channels <sup>87</sup>	150-600 mg per day	Dizziness, drowsiness, peripheral oedema, ataxia, weight gain	None	Guidelines focused on neuropathic pain of any cause and not on ALS
Tricyclic antidepressants <sup>78</sup>	EFNS guidelines	N/A	Effective in various causes of neuropathic pain			50-100 mg per day	Dry mouth, blurry vision, constipation, urinary retention, drowsiness	Cardiac arrhythmias; prolonged Q-T interval; prostate hypertrophy; closed angle glaucoma	Guidelines focused on neuropathic pain of any cause and not on ALS
<b>Cramps (lower limbs, hands, abdomen)*</b>									
Quinine sulphate <sup>88</sup>	Systematic review of clinical trials	1,586 participants with cramps of any cause	Significant reduction in cramp number (28%; 95% CI 15–40%), intensity (10%; 4–16%), and days (20%; 6–33%) over 2 weeks			250-500 mg per day	Significantly more minor adverse events in treatment group (risk difference +3%, 95% CI 0% to 6%)	Cardiac arrhythmias; bradycardia; prolonged Q-T interval; liver or renal dysfunction; hypokalemia	FDA and AAN have issued safety concerns about use of quinine sulphate for cramps <sup>89</sup>
Gabapentin <sup>90</sup>	Phase 3 randomised	204 patients with ALS	No effect on muscle cramps			900-3600 mg per day	Safe and well tolerated. More	None	Pain was not an outcome



	double-blind trial		after 9 months				common side effects in gabapentin treated patients were light headedness, drowsiness, falls and limb swelling		measure in this study
Mexiletine <sup>91</sup>	Phase 2 randomised placebo-controlled study	60 patients with ALS	Significant dose-dependent reductions in cramp frequency (300 mg per day: 31%, p=0.047; 900 mg per day: 16%, p=0.002) and intensity (300 mg per day: 45%, p=0.08; 900 mg per day: 25%, p=0.005)			300-900 mg per day	Safe and well tolerated at 300 mg per day; adverse effects at 900 mg per day led to high rate of discontinuation	Cardiac arrhythmias; atrioventricular block	Pain was not an outcome measure in this study
Tetrahydrocannabinol <sup>92</sup>	Phase 2 randomized double-blind crossover trial	27 patients with ALS	No effect on cramp intensity and number			5 mg bid	Two non-drug related serious side effects, one patient had mild dizziness	Co-morbid mental disorders	Pain was not an outcome measure in this study
Levetiracetam <sup>93</sup>	Open-label pilot trial	20 patients with ALS	Significant reduction in cramps after 9 months (1500 mg bid, reduction of the Cramp Severity Scale score, p<0.01)			1500 mg bid	Fatigue, somnolence, headache, insomnia	Severe mood depression	Pain was not an outcome measure in this study
<b>Spasticity (lower limbs)*</b>									
Levetiracetam <sup>93</sup>	Open-label pilot trial	20 patients with ALS	Significant reduction in spasticity after			1500-3000 mg per day	Fatigue, somnolence, headache,	None	Pain was not an outcome measure in

			9 months (1500 mg bid, reduction of the Penn Spam score, p<0.001)				insomnia		this study
Intrathecal baclofen <sup>94</sup>	Case series	8 patients with ALS	Average of 54% reduction in post-operative pain intensity (p=0.0082)			25-50 microg per day	None reported by the authors. Possible side effects are somnolence, hypotonia, headache, nausea, vomit, vertigo	Not reported	Intractable spasticity not defined
Baclofen (oral), tizanidine, dantrolene, benzodiazepines <sup>95</sup>	Observational study of Italian neurological centres	36 ALS neurological departments	Effectiveness not reported			N/A	N/A	N/A	Study of clinical care, not effectiveness of treatments
<b>Pain caused by inability to move and change position (diffuse, including buttocks, limbs, and trunk)†</b>									
NSAIDs and acetaminophen <sup>51</sup>	Observational study	42 ALS patients, 27 with pain	Partial or complete relief in 15 patients (55.5%). Not reported in detail types of drugs and doses			Depends on the type of drug	Side effects not reported by the authors. Possible side effects are gastrointestinal disturbances; risk of gastric ulcer	Positive history of allergic reactions to drugs; severe heart failure	First-line treatment
Opioids <sup>96</sup>	Observational study	124 patients with ALS admitted to an hospice	Effective, especially in advanced disease (36 of 49 [73%] patients had a good response)			30 (+/- 2.34) mg per day oral morphine equivalent	Constipation; nausea; vomit	Not reported	Second-line treatment
Cannabis <sup>97</sup>	Survey	131 patients with ALS	Moderately effective (no statistics provided)			Not reported	Amotivational syndrome; tachycardia; confusion	Not reported	Only 10% of respondents used cannabis
<b>Paresis of limbs (shoulder pain, articular pain)†</b>									
Joint injections with lidocaine and	Systematic review of	240 participants with shoulder	Intra-articular injections with			Triamcinolone 20 mg + 1 ml	Not reported	Not reported	The review does not

steroids <sup>98</sup>	clinical trials	pain of any cause (2 trials)	lidocaine and steroids better than physiotherapy			2% lidocaine			include ALS patients
Intra-articular steroid injection vs physiotherapy (mobilization, exercise and electrotherapy) <sup>98</sup>	Systematic review of clinical trials	109 participants with adhesive capsulitis (2 trials)	Steroid injections more effective than physiotherapy			Triamcinolone 20 mg	Pain after treatment, skin irritation, facial flushing	Not reported	The review does not include ALS patients

*In view of the evidence, the Practice Parameters of the American Academy of Neurology<sup>22</sup> and the European guidelines on the Clinical Management of ALS recommend that pain management in ALS is based on clinical experience.<sup>23</sup> \*Primary forms of pain. †Secondary (mainly nociceptive) forms of pain. NSAIDs, non-steroidal anti-inflammatory agents. All studies involving ALS patients have been reviewed. When no studies on ALS patients were available, the most recent general reviews or expert opinions on the topic have been reported.*

### ***Pharmacological treatments (Table 1)***

A recent Cochrane review<sup>24</sup> assessed the efficacy of pharmacological treatment for primary and secondary pain in ALS based on the analysis of case series with more than 5 patients published up till 2012, along with several other case series reporting less than five patients. The authors concluded that there was no evidence from randomized controlled trials (RCTs) about the management of pain in ALS. In two surveys on ALS centres the most commonly used drugs for pain in ALS were NSAIDs and acetaminophen for secondary pain, and medications for primary neuropathic pain (gabapentin, pregabalin, tricyclic antidepressants).<sup>95,99</sup> Opioids were the second option when pain was not controlled. Opioids are required particularly in advanced stages to control increased pain and symptoms related to respiratory insufficiency, such as dyspnoea and poor sleep. However, the review<sup>24</sup> emphasized the lack of reliable data for use of opioids in ALS that was even more evident for the analysis of efficacy. There is indeed no study in patients with ALS on the drugs recommended for neuropathic pain,<sup>78</sup> and only two surveys on the use of cannabinoids for neuropathic and nociceptive pain.<sup>97,100</sup> Cannabis may be effective in reducing pain, and can act in synergy with opioids. Although of interest from an epidemiological perspective, these surveys cannot provide information for clinical practice. Thus, the current management of pain in ALS remains based on physicians' experience rather than on proper guidelines, as reflected in the recommendations provided by the Practice Parameters of the American Academy of Neurology<sup>22</sup> and the European guidelines on the Clinical Management of ALS.<sup>23</sup>

Data from surveys, open and randomized clinical trials are available on the treatment of cramps in ALS. Quinine sulphate is the most used drug for cramps, though with caution for several possible serious side effects (e.g. thrombocytopenia) and drug interactions.<sup>99</sup> In U.S. Food and Drug Administration has issued safety announcements that quinine sulphate is only approved for the

treatment of malaria and not approved for the treatment or prevention of leg cramps (Baldinger et al). The superior efficacy of quinine sulphate against cramps compared to placebo or other interventions has been suggested in a Cochrane review that included several etiologies,<sup>88</sup> but studies of the effects of quinine sulphate on cramps in ALS specifically have not been done.<sup>89</sup> A recent phase II randomized placebo-controlled study showed that treatment with mexiletine resulted in a significant dose-dependent reduction in muscle cramp frequency and severity and was well tolerated at the dose of 300 mg/d.<sup>91</sup> Conversely, a randomized, double-blind, placebo-controlled crossover trial on tetrahydrocannabinol given at the dose of 5 mg bid failed to demonstrate an efficacy on cramps in ALS, although the drug was well tolerated.<sup>92</sup> Gabapentin did not demonstrate efficacy in slowing the rate of muscle strength decline in ALS patients and in this context no efficacy against cramps was reported.<sup>90</sup> A study reported a possible positive effect of levetiracetam on cramps and spasticity in ALS, but this finding is limited by the non-controlled and open design of the trial.<sup>93</sup>

There is no controlled clinical trial on the efficacy of drugs to treat spasticity in ALS. Most ALS physicians in Italy use baclofen, followed by tizanidine, benzodiazepines and dantrolene.<sup>95</sup> Another European survey reported the widespread use of carbamazepine.<sup>99</sup> A small study on 8 patients with spasticity-related intractable pain referred for intrathecal baclofen (ITB) pump placement reported a 54% average reduction in post-operative pain intensity based on a 0 to 10 rating score in six patients.<sup>94</sup> This finding is limited, however, by the open-label design of the study and by the lack of follow-up data precluding analysis of ITB's long-term efficacy on pain.

### ***Non-pharmacological treatments*** (Table 2)

Regular stretching and passive and/or active range-of-motion exercises are safe and effective in preventing spasticity.<sup>101</sup> These approaches are also useful for treating secondary pain resulting

from motor degeneration, including musculoskeletal pain, and for maintaining muscle length and physical mobility.<sup>101</sup> For example, a timely, regular program of stretching and range-of-motion exercises could prevent occurrence of shoulder pain.<sup>101</sup> An open-label, randomized, parallel study (NCT01521728) on resistance and endurance exercise, and stretching/range-of-motion in a series of ALS patients has been recently completed and its results are awaited. Osteopathic manual treatment showed some efficacy in the treatment of pain in a small open-label study.<sup>102</sup> Other less commonly used interventions for secondary forms of pain include warm and cold compresses, transcutaneous electrical nerve stimulation, acupuncture, joint injections with lidocaine and steroids.<sup>98,103</sup> Many types of assistive devices can be used to prevent pain caused by reduced mobility, including special mattresses and pillows, and custom-fitted wheelchairs. Neutral position splints for hands and ankles are effective in reducing joint contractures.<sup>101</sup> Patients and caregivers should be trained to appropriately use transfer techniques and devices like canes and walkers in order to prevent falls and injuries. Remedies for complications related to NIV include changing the mask before the appearance of pressure-related skin changes (e.g. using nasal mask or pillows during the day and orofacial mask during the night) and use of special dermal application materials.<sup>104</sup>

The interest in alternative therapies is increasing in recent years and is particularly popular in Eastern countries.<sup>105-107</sup> In China, there is widespread use in ALS patients of integrative therapies such as vitamins, herb decoctions and compounds, acupuncture, yoga, and massage therapy.<sup>107</sup> The efficacy of these therapies in relieving symptoms, in particular pain, has not been studied yet.

**Table 2: Studies of clinical use and effectiveness of non-pharmacological strategies for pain in ALS**

	Study design	Number of patients/centres	Results	Contraindications	Comments
<b>Cramps (lower limbs, hands, abdomen)*</b>					
Stretching <sup>101</sup>	Review of published work and case studies	3 patients with ALS	Clinically effective	Not reported	Based mainly on clinical experience
Massaging <sup>108</sup>	Review of published work	N/A	Clinically effective	Not reported	Based mainly on clinical experience
<b>Spasticity (lower limbs)*</b>					
Moderate physical activity <sup>109</sup>	Randomised trial	25 patients with ALS	Significantly less deterioration on ALS Functional Rating Scale ( $p<0.001$ ) and Ashworth Spasticity Scale ( $p=0.005$ ) after 3 months but no difference after 6 months. No effect on pain	None reported	
Daily stretching, assistive ROM exercises <sup>101</sup>	Review of published work and case studies	3 patients with ALS	Clinically effective	Avoid high-resistance exercise, select a mode of exercise with minimal risk of injury from falling	Based mainly on clinical experience
<b>Pain caused by inability to move and change position (diffuse, including buttocks, limbs and trunk)†</b>					
Osteopathic manual treatment <sup>102</sup>	Feasibility pilot study	14 patients with ALS	Single-blind trial comparing osteopathic manual treatment (OMT) vs usual care followed by an OMT open period. Mild reduction of pain at the Pain Severity Index ( $p=0.05$ )	None reported	Small pilot study
Daily stretching, assistive ROM exercises, wheelchairs, orthoses <sup>101</sup>	Review of published work and case studies	3 patients with ALS	Clinically effective	Avoid high-resistance exercise, select a mode of exercise with minimal risk of injury from falling	Based mainly on clinical experience
<b>Paresis of limbs (shoulder pain, articular pain)†</b>					
Range of physiotherapy interventions (e.g., transcutaneous	Systematic review of clinical trials	Ultrasound vs. placebo (general shoulder pain, 73 treated, 72 placebo) Ultrasound vs. placebo (calcific	Ultrasound vs. placebo (general shoulder pain): non effective Ultrasound vs. placebo (calcific tendinitis): moderately effective (risk		Varied quality of trials prevented firm conclusions from being drawn

electrical nerve stimulation, stretching, range-of motion, massage, laser therapy) <sup>98</sup>		tendinitis, 32 treated, 29 placebo) Supervised exercises (rotator cuff disease, 45 treated, 28 placebo) Laser therapy (adhesive capsulitis, 20 treated, 20 placebo) Laser therapy (2 trials, supraspinatus tendinitis, 28 treated, 24 placebo) Iontophoresis with acetic acid plus ultrasound (11 treated, 10 not treated) Mobilization plus exercise vs exercise alone (17 vs 17) Isokinetic resistance exercises vs. electromyographic biofeedback (11 vs 9)	ratio, 4.53) Supervised exercises: moderately effective (risk ratio, 2.45) Laser therapy (adhesive tendinitis): effective (risk ratio, 8.00) Laser therapy (supraspinatus tendinitis): not effective Iontophoresis with acetic acid plus ultrasound (calcific tendinitis): not effective Mobilization plus exercise vs exercise alone (adhesive capsulitis and rotator cuff impingement): no difference Isokinetic resistance exercises vs. electromyographic biofeedback (anterior instability): no difference		
Acupuncture <sup>103</sup>	Systematic review of clinical trials	9 trials of participants with shoulder pain of any cause (n≥18 in each study)	Evidence suggests no effect or possible short-term benefit (over 2–4 weeks).	None reported	Varied quality of trials prevented firm conclusions from being drawn
Assistive ROM exercises <sup>101</sup>	Review of published work and case studies	3 patients with ALS	Clinically effective	Caregiver participation needed when muscle weakness prevents the patient from performing program independently	Based mainly on clinical experience
<b>Joint contractures (hand and ankle joints)†</b>					
Neutral-position splints for hands and ankles <sup>101</sup>	Review of published work and case studies	3 patients with ALS	Can supplement stretching and ROM exercises	None reported	Based mainly on clinical experience

*In view of the evidence, the Practice Parameters of the American Academy of Neurology<sup>22</sup> and the European guidelines on the Clinical Management of ALS recommend that pain management in ALS is based on clinical experience.<sup>23</sup> \*Primary forms of pain. †Secondary (mainly nociceptive) forms of pain. ROM, range of motion.*

*All studies involving ALS patients have been reviewed. When no studies on ALS patients were available, the most recent general reviews on the topic have been reported*



## Conclusions and future perspectives

ALS patients can suffer from pain due to a variety of causes including reduced mobility, cramps and spasticity. On the basis of the available literature, pain should be considered as a condition that: 1) can complicate the course of ALS in a percentage of patients that varies according to the definition of pain used and the analysis or not of mood comorbidities, 2) can occur throughout the course of the disease, 3) commonly has a mild intensity, with the possible exception of late-stages of the disease, and 4) can significantly undermine, along with depression, patients' quality of life.

The prevalence of pain in ALS is still not completely clear, due both to the scarcity of focused studies and the heterogeneous methodologies used. Longitudinal studies on onset and course of pain and cramps in large series of patients are therefore needed, as are studies focused on the impact of co-morbid cognitive impairment on pain perception, which might affect the results of epidemiological studies. Moreover, research aiming to identify the individual susceptibility of ALS patients to develop chronic pain including risk relating to personal, socioeconomic, genetic and disease-related factors is needed. Pain may be more frequent in patients with spinal presentation,<sup>14,15,41</sup> but the lack of predictive biomarkers hinders the possibility of identifying those patients at higher risk. Another area to consider in future ALS studies is the assessment of different types of pain (e.g. neuropathic, nociceptive) and the role of central sensitization, and their prevalence and impact on patients' management and quality of life during the course of the disease. It would also be useful to understand factors that influence disease prognosis, such as sensory changes.

The heterogeneity of the mechanisms at the base of the diverse manifestations of pain in ALS, and the variable and unpredictable progression of the disease, underscores the need for an individually tailored and multidisciplinary approach to its management. Careful and timely evaluations are necessary for a correct management of pain, particularly in the later stages when patients experience respiratory failure and severe reduced mobility. Guidelines on pain ascertainment, including the identification of rating scales to be used in the clinical setting are needed. The frequent association between pain and depression can further worsen the quality of life of ALS patients. Thus, a thorough knowledge of the patient's physical and psychological conditions, including anxiety and emotional lability, is essential for the management of each patient as an individual. Pharmacological treatment can be useful for some primary pain types, mainly neuropathic, and physical therapy may have a role in preventing and treating pain in ALS.

Pain treatment has also positive psychological effects on ALS patients, thus affecting patient and carer quality of life. However, specific guidelines on the management of pain in ALS patients are lacking, and the results of the few clinical trials published on cramps and spasticity were disappointing. Several treatments often used by patients to relieve pain, both prescribed by physicians and self-prescribed, including physical therapy approaches and non-conventional treatments, never underwent formal randomized trials. Trials on both pharmacological and non-pharmacological treatments in different types of pain with appropriate methodology and outcome measures are therefore warranted to evaluate safety and establish efficacy. Pharmacogenomics studies would be also useful to identify gene variants associated with different response to analgesics and side effects. When the classical placebo-controlled double-blind design is not feasible, for example in evaluating non-pharmacological treatments, alternative designs should be considered, such as the use of waiting list controls<sup>110</sup> or blinded assessment of outcome.<sup>111</sup> Until results from more robust treatment studies are available, treatment should be based on good clinical practice backed up by available guidelines on non-malignant chronic pain.

## **Contributors**

AC coordinated authors' writing, revision, and editing, wrote the first draft, and finalized the manuscript. AC did the literature search and contributed to sections on epidemiology of pain, assessment of pain in the clinical setting, characteristics of pain in ALS and relation to comorbidities, Table 2, and the description of case study 1; GL did the literature search and contributed to sections on mechanisms of pain, pain and ALS genetics, Table 1, and the description of case study 2; GM did the literature search and contributed to the section on treatment and the description of case study 3. All authors were involved in critical revision of the manuscript and in the preparation of the Figure.

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## **Search strategy and selection criteria**

We searched PubMed (1966, to October 25, 2016), Embase (1980, to October 25, 2016), and the Cochrane Library (April, 1996, to October 25, 2016) for relevant titles using the terms "amyotrophic lateral sclerosis" or "motor neuron disease" or "primary lateral sclerosis" in combination with "pain", "sensory symptoms", "cramps", "pain therapy", and "opioids". Further

material was gathered from reference lists, review articles, and major textbook chapters. We also included abstracts and reports from relevant meetings. The final reference list was generated on the basis of originality and relevance to the topics covered in this report. Emphasis was placed on publications from the past 10 years, but we did not exclude commonly referenced and highly regarded older publications.

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### **Panel 1: Case study**

A 47-year-old man reported painful cramps in the last 2 years, involving lower limbs, feet and abdomen. The cramps were more frequent during activity, forcing the subject to interrupt the movement, and when falling asleep. The cramps had been unsuccessfully treated by patient's general practitioner with potassium and magnesium supplements, and by muscle relaxing massages. Two months before the neurological consultation, the patients started feeling weakness and mild hypotrophy in the calves and anterolateral aspect of the legs bilaterally. The cramps were getting increasingly severe, and sometimes appeared also at rest. The neurological examination found diffuse deep tendon hyperreflexia, positive Babinski and Hoffmann signs and diffuse fasciculations. Needle electromyography showed diffuse spontaneous activity and chronic neurogenic changes in lower limbs. Brain and spinal cord MRI were normal. Creatine kinase was mildly elevated. A diagnosis of ALS was done and the patients started riluzole at the dose of 100 mg daily. After having excluded the presence of disturbances of the cardiac rhythm, the patient was treated with quinine sulphate 250 mg at bedtime that provided a substantial reduction of cramp frequency and intensity.

## Panel 2: Case study

A 57-year-old woman was referred for a 3-year history started with pain in the left sole with proximal progression to both the lower limbs followed by impaired gait with need of assistance for climbing the stairs, lower limb weakness and behavioural changes with irritability and emotional lability. She had fallen five times in the last year. Family history was negative and she did not report known consanguinity up to the grandparents. The neurological examination showed paraparesis and moderate spasticity of the left lower limb, weakness of the distal muscle of the upper limbs and of both proximal and distal muscle of the lower limbs, diffuse deep tendon hyperreflexia, positive Babinski and Hoffmann signs, reduced pinprick sensation with a stocking distribution and absent vibratory sensation at the first metatarsal joint using the 64 Hz Rydel-Seiffer tuning fork. Needle electromyography showed diffuse spontaneous activity and chronic neurogenic changes. Nerve conduction studies showed reduced amplitude of compound muscle action potential amplitudes with normal conduction velocities, whereas sensory nerve action potentials and conduction velocities were normal. Somatosensory evoked potentials recorded by stimulating the upper limbs were normal and showed increased central conduction latency by stimulating the lower limbs. Motor evoked potentials were normal recording from the upper limbs and showed increased central conduction latency from the lower limbs. Skin biopsy showed reduced intraepidermal nerve fibre density compared to age and sex-adjusted normative values. A diagnosis of neuropathic pain was therefore considered. Brain and spinal cord magnetic resonance imaging studies were normal. The genetic study revealed the p.N65S mutation in *SOD1* gene. ALS was diagnosed and riluzole 100 mg daily started. She was taking pregabalin 150 mg and tramadol 50 mg daily. At follow-up visits, besides the progressive motor impairment, the patients complained of persistent and severe pain in the lower limbs scored 7 at the visual analogue scale. Pregabalin and tramadol were suspended and amitriptyline was progressively increased up to 50 mg daily, which provided 50% of pain intensity reduction that the patient reported as a satisfactory relief.

### **Panel 3: Case study**

A 56-years-old came to our attention after a 3-year history of ALS. He presented a classic phenotype with moderate dysarthria, swallowing problems requiring soft diet, paresis of the 4 limbs with spasticity in the lower limbs and no symptom or sign of respiratory failure. Transfers required some aid. Gait was possible with a walker but for short distances (few metres). His major complaint was disturbed sleep with frequent arousals due to diffuse pain, in particular neck, shoulders and back. The clinical characteristics of pain in this patients pointed toward a potential diagnosis of nociceptive pain. The only medication was riluzole; an attempt with the hypnotic medication zolpidem had been interrupted because of no efficacy. He followed physical therapy only occasionally. At the visit, both shoulders had a limited excursion, and passive movements elicited acute pain; lower limbs showed marked spasticity. The patient was addressed to daily sessions of physiotherapy with active/passive range of motion and stretching exercises; the caregiver was trained in transfer techniques. Baclofen at increasing dosage demonstrated efficacy in reducing spasticity and enabled the patients to maintain the postures in bed for longer time. The prescription of a mattress of viscoelastic foam also improved the quality of sleep. The adjunct of tizanidine was aborted for excessive daily somnolence even at low dose. An attempt with cannabinoids (Sativex® oromucosal spray, 3 ml/day, corresponding to delta-9-terahydrocannabinol 81 mg plus cannabidiol 75 mg) was not tolerated for the occurrence of dizziness and confusion. A combination of acetaminophen plus codeine provided a satisfactory pain relief.

### **Figure legend**

Graphic description of types of pain in ALS. All reported types of pain are secondary in nature (mainly nociceptive), with the exception of neuropathic pain. Green shading=primary pain. Blue shading=secondary (mainly nociceptive) pain.